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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/667,947	09/22/2000	Stephen James Russell	07039-298001	9619

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 02/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/667,947	Applicant(s) Russell et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 18, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *"Raw sequence listing" & "Notice to comply..."*

DETAILED ACTION

Applicants' amendment filed 12-18-02 has been entered. Claims 1-26 have been canceled. Claims 27-58 have been added. Claims 27-58 are pending and under consideration.

The sequence listing filed 12-18-02 has been entered. However, the content of the computer readable form does not comply with the requirement of 37 C.F.R. 1.822 and/or 1.823. Please see the attached "Notice to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosure" and "Raw sequence listing". Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 27-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 12-18-02 necessitates this new ground of rejection.

The phrase "monitoring gene expression...detecting the amount of said heterologous polypeptide in said biological fluid, thereby providing an indication of the amount of said gene expression" in claim 27 is vague and renders the claim indefinite. It is unclear the "gene" expression means expression of the gene encoding the heterologous polypeptide or it means expression of genes other than the gene encoding the heterologous polypeptide. If the latter is the

case, it is unclear how the gene is connected to the gene encoding said heterologous polypeptide. Claims 28-42 depend on claim 27 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 27-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants' amendment filed 12-18-02 necessitates this new ground of rejection.

Claims 27-42 are directed to a method of monitoring gene expression from virus infected cells within an organism comprising administering to said organism a Paramyxoviridae virus, such as Paramyxovirus, Morbillivirus, Rubulavirus, and Pneumovirus, containing a nucleic acid encoding a heterologous polypeptide, such as CEA, tumor antigen and beta subunit of human choronic gonadotrophin, and detecting the amount of said heterologous polypeptide in said biological fluid, thereby providing an indication of the amount of said gene expression. Claims 28 and 29 specify the heterologous polypeptide is biologically inactive and below 10 kDa, respectively. Claims 33-36 specify the nucleic acid encodes a recombinant fusion protein comprising said heterologous polypeptide fused to an endogenous polypeptide, such as H protein,

and a protease cleavage site as an amino acid linker. Claim 37 specifies the Paramyxoviridae virus is replication-competent. Claims 43-58 are directed to a Paramyxoviridae virus comprising a nucleic acid encoding a heterologous polypeptide as set forth above.

The specification generates Measles Virus (MV) for enhancing fusogenecity by modifying MV F, H, or M protein, recombinant MV expressing single chain antibody (ScAb) against CD38 or CEA on the surface of the virus to alter targeting specificity, and shows co-expression of F protein with chimeric HXL (long linker arm between H protein and scAb) in MC38-CEA cells led to extensive syncytia formation.

As discussed above under 35 U.S.C. 112 second rejection, it is unclear the "gene" expression means expression of the gene encoding the heterologous polypeptide or it means expression of genes other than the gene encoding the heterologous polypeptide. If the latter is the case, it is unclear how the gene is connected to the gene encoding said heterologous polypeptide. The specification fails to provide the correlation between the gene whose expression is going to be monitored and the gene encoding the heterologous polypeptide. The specification also fails to provide adequate guidance and evidence for how detecting the amount of the heterologous polypeptide in a biological fluid from an organism could provide an indication of the amount of a gene expression. When the gene whose expression is monitored is under different gene expression control from the gene encoding the heterologous polypeptide, there is no correlation between the expression of the monitored gene and the expression of the heterologous polypeptide. There is no evidence of record that detection of a certain amount of the

heterologous polypeptide in a biological fluid would provide indication of the amount of gene expression of the monitored gene within an organism. Absent such correlation and evidence, one skilled in the art at the time of the invention would not know whether detection of a heterologous polypeptide in a biological fluid would provide indication of the amount of gene expression of the monitored gene within an organism.

The claims encompass using various promoter for the expression of the heterologous polypeptide and the monitored gene expression via various administration routes of the paramyxoviridae virus to an organism. The specification fails to provide adequate guidance and evidence whether there is any detectable heterologous polypeptide in a biological fluid when the recombinant Paramyxoviridae virus is administered intratumorally or locally into the brain in which the virus will likely stay in the tumor or locally in the brain. Further, different promoters have different expression patterns in various tissues or cell types *in vivo*. The specification fails to provide adequate guidance and evidence that introduction of Paramyxoviridae viruses expressing a heterologous polypeptide under the control of various promoters to an organism via various administration routes could provide sufficient expression of said heterologous polypeptide *in vivo* and sufficient heterologous polypeptide is released to biological fluid for detection, and the amount of said heterologous polypeptide is indicative of the amount of monitored gene expression. There is no evidence of record that the expressed heterologous polypeptide in the recombinant Paramyxoviridae virus would be present or sufficient detectable heterologous polypeptide would be present in the biological fluid, such as blood, urine, saliva

etc., and the detection of said heterologous polypeptide would be indicative of the amount of the monitored gene expression *in vivo*.

The specification discloses the use of the claimed Paramyxoviridae viruses for monitoring gene expression for virus infected cells within an organism, however, the specification fails to provide sufficient enabling disclosure for such use for the reasons as set forth above under 35 U.S.C. 112 first paragraph. Thus, the specification fails to enable the claimed Pramyxoviridae viruses and one skilled in the art at the time of the invention would not know how to use the claimed Paramyxoviridae viruses.

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed invention to monitor gene expression of interest and would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

a person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 43, 53, 54 and 58 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kirn et al., 1996 (Molecular Medicine Today, 2(12): 519-527, IDS-AGGG). Applicants' amendment filed 12-18-02 necessitates this new ground of rejection.

Claims 43, 53, 54 and 58 are directed to a Paramyxoviridae virus, such as a Newcastle disease virus, comprising a nucleic acid sequence encoding a heterologous polypeptide. Claim 53 specifies the Paramyxoviridae virus is replication-competent.

Kirn teaches that replication-competent viruses are used as selective cancer therapeutics and the specific viruses used include tumor-targeting herpes simplex viruses, Newcastle disease viruses and adenoviruses. Infection of a tumor cell with a replicating virus can increase the sensitivity of the cell to killing by cytokines such as TNF-alpha and interferon alpha. Kirn also teaches that addition of cytokine gene, such as IL-2, to replicating virus genome can increase tumor killing effect (e.g. abstract, box 2, p. 521). Thus, claims 43, 53, 54 and 58 are rejected

under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kirn et al., 1996.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 43, 44, 53, 54 and 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Singh et al., January 1999 (Journal of General Virology, Vol. 80, p. 101-106).

Claims 43, 44, 53, 54 and 56 are directed to a Paramyxoviridae virus, such as a Newcastle disease virus, comprising a nucleic acid sequence encoding a heterologous polypeptide, such as a biologically inactive polypeptide. Claim 53 specifies the Paramyxoviridae virus is replication-competent.

Singh teaches generation of a measles virus (MV) that expresses biologically active human IL-12 by inserting the coding sequence of the two subunits of human IL-12 separated by an IRES and between H and L genes of MV (e.g. abstract, Fig. 1). Singh also teaches making a recombinant MV expressing marker genes such as green fluorescence protein (GFP), beta-galactosidase and chloramphenicol acetyltransferase (CAT), which are biologically inactive (e.g.

p. 103). IL-2, GFP, beta-galactosidase and CAT are heterologous polypeptides. Thus, claims 43, 44, 53, 54 and 56 are anticipated by Singh.

It should be noted that claims 43-58 are product claims and the intended use of the products does not carry weight in 35 U.S.C. 102 or 103 rejections.

Conclusion

No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.